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The Upper Respiratory Tract: Mucous Membrane Irritation

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Despite the widespread recognition that mucosal irritation is a cardinal feature of "sick-building syndrome," few data exist on the cause, natural history, or pathophysiology of upper respiratory mucous membrane irritation. The baseline prevalence of nasal symptoms among building occupants is often 20%, but in some studies it is as high as 50 to 60%. New techniques of nasal challenge and analysis of cells and mediators in nasal lavage fluid have proved useful in the assessment of rhinitis caused by antigens, cold air, and viruses, and these techniques are now being applied to the study the response to irritants. Human inhalation challenge studies have recently demonstrated a spectrum of sensitivity to environmental tobacco smoke, but the basis for this difference requires additional investigation. Animal and *in vitro* studies indicate that the chemosensitive neurons and airway epithelium may be critical targets for irritants that participate in the induction of inflammation. New research methods are needed, particularly to evaluate complaints of nasal congestion, drying, and irritation. Techniques should be developed that may be useful for field studies, where the health effects of a complex mixture are being assessed in a specific indoor environment. There exists a group of individuals who report a variety of symptoms on exposure to low levels of common volatile organic mixtures such as perfume, cigarette smoke, and cleaning agents. Some of these individuals report having occupied "sick buildings" during the time their symptoms began. Research is needed to understand the basis of their complaints, their etiology, and treatment.

Introduction

The upper respiratory tract serves many important functions, including the warming and humidification of inspired air and removal of particle and vapor-phase pollutants. The nose is also a major site of common allergic illnesses, the site of infection with common viruses and a site for mucosal irritation and nonallergic inflammation (*2*). Risk assessment has historically used excess mortality, cancer, or birth defects as the primary health effects (*3*). The problem of upper respiratory tract disease is not trivial, since billions of dollars each year are spent to relieve upper respiratory symptoms of rhinorrhea and congestion (*4*). For the upper respiratory tract, however, illness and discomfort but not mortality are the primary recognized health effects. These health risks are harder to quantify, and new methodology may be needed for risk assessment.

The purpose of this paper is to review the evidence that upper respiratory tract mucous membrane irritation occurs in indoor environments, to describe research methods available to study upper respiratory effects, and to identify needs for new research methods and gaps in current research.

Clinical experience and epidemiologic studies are two useful sources of information to answer the question: Does mucous membrane irritation occur in indoor environments? The original World Health Organization definition of "sick-building syndrome" was a consensus of clinical experience. The definition of sick-building syndrome was irritation of the eye, nose, and throat; dry mucous membranes and skin; erythema; mental fatigue and headache; airway infections and cough; hoarseness of the voice and wheezing; unspecific hyperreactivity reactions; and nausea and dizziness (*1*). Mucous membrane irritation has continued to be a recurrent feature of indoor air complaints (*5*).

The baseline prevalence of nasal symptoms among building occupants varies with many factors, including the precise wording of the question in the survey. For example, some surveys ask about the frequency of nasal irritation in the past year, while others ask about the past month, or only the day of the study. Some define "yes" as irritation that is present "often" or "always," while other investigators define "yes" as a symptom that is present "sometimes." Other surveys define work-related irritation only when symptoms are absent in the morning and begin each day after arriving at work. This definition may exclude individuals with chronic irritation related to the workplace. Irritation can refer to a symptom or the inflammation caused by an irritant. As a result of these differences, caution must be exercised in comparing prevalence rates between studies.

There are a group of upper respiratory symptoms that may occur after exposure to an irritant but also may be caused by other diseases. These symptoms include throat and nose irritation, nasal congestion, rhinorrhea (runny nose), postnasal drip, nasal drying, sneezing, and hoarseness. Epidemiologic research is needed to determine effective methods for grouping these symptoms. For example, the technique of principal components analysis could suggest logical groupings for statistical analysis. As a broad generalization, rates of nasal irritation, runny nose, or nasal congestion are often around 20%, but can be as high as 50 to 60% (*5–7*).

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Although the exact prevalence of upper respiratory mucosal irritation symptoms may vary, it is clear that there is a spectrum of symptoms in populations that have been studied. The basis for the differential responsiveness is unknown. It is unknown whether symptomatic individuals are a sensitive subgroup (i.e., reacting at a lower than usual dose, but in a similar manner to nonsensitive individuals) or sensitized (i.e., reacting in a manner that would not occur at any dose in the nonsensitized individual). It is unknown whether differential responsiveness results from preexisting disease or is an inherited trait. It is also unknown whether the same distribution of responsiveness between individuals exists for all irritants and irritant mixtures.

Three major epidemiologic studies in the mid-1980s profiled health complaints of more than 9000 people and building characteristics of more than 50 buildings (*8–10*). Features of the buildings, materials, and characteristics of occupants were related to mucosal irritant symptom prevalence. In one or more studies, symptoms were higher in buildings with a higher occupancy rate, with use of carbonless copy paper, with high estimated office surface areas, and with a high fleece factor (reflecting the presence of a surface onto which irritants or bioaerosols could adsorb). Buildings with natural ventilation had lower symptom rates than those with mechanical systems that used chillers and humidifiers. Women had higher symptom rates than men, and clerical/secretarial workers had higher rates than managers. It is unknown whether the higher rates in women reflect differential reporting of similar health events, different susceptibility to similar exposures, or different exposures related to job category or job performance.

There are important clinical questions that derive from the recognition that mucous membrane irritation occurs in indoor environments. Physicians need answers to these questions to assess individual complaints and to advise their patients as to whether to continue working in a building where symptoms are occurring. The fundamental question is: Does exposure to complex mixtures in the indoor environment alter peoples' health? First, what are the long-term consequences of mucous membrane irritation? Second, does the presence of symptoms of increased mucous membrane irritation indicate an increased risk of inflammation compared with asymptomatic individuals? Finally, does increased inflammation indicate an increased risk of organ system damage? The answers to these questions are largely unknown at present, and practical approaches for the treating physician are lacking.

A study of the pathogenesis of mucous membrane irritation in indoor environments must focus on slightly different issues. The broad research question is: Is there evidence that exposure to complex mixtures will alter upper respiratory biology or physiology? More specific questions are: What mixtures are commonly found in indoor environments and what factors determine the irritant properties of these mixtures? What part of the upper respiratory tract is a target organ for exposure to complex mixtures? Does differential responsiveness alter a subject's dose of a mixture? How is irritation perceived and how can it be measured? What host factors modulate mucous membrane irritation? What is the time course, natural history, and sequelae of an irritant exposure? Does increased acute responsiveness reflect increased risk of chronic disease?

The following discussion of mucous membrane irritation details the constituents of the nasal mucosa and then presents results focusing on exposures to three substances: tobacco smoke, acrolein, and ozone. These are examples of substances for which mucosal responses are thought not to act via an IgE mechanism. Human studies, *in vitro* studies, and animal studies are presented that illustrate differential responsiveness and indicate target tissues and possible pathogenetic mechanisms of irritant responses. Tobacco smoke is a complex mixture that contains both oxidants and aldehydes. Acrolein is an aldehyde and is a well-recognized irritant. Ozone is both an outdoor and indoor air pollutant and is an example of an oxidant that has irritant properties.

Nasal Mucosa

The nasal mucosa has many components, all of which are potential targets for irritant exposure (*2*). A protein-rich mucous layer is generated by secretory products from submucosal glands and secretory cells, with water and solutes provided by epithelial ion transport. The nasal epithelium at the entrance to the nose is a stratified squamous epithelium, but changes within a few centimeters to pseudostratified ciliated columnar epithelium. The epithelium is composed of ciliated, secretory, and basal cells. Situated in the submucosa is a complex vascular supply that can undergo rapid changes in blood volume. Sympathetic, parasympathetic, and unmyelinated chemosensitive c-fiber neurons ramify extensively throughout the mucosa, with projections to the epithelium, glands, and blood vessels. Inflammatory cells, including neutrophils, eosinophils, basophils and mast cells, and mononuclear cells may be present on the airway surface, in the epithelium, or the submocosa.

The irritant properties in indoor mixtures undoubtedly are related in part to physicochemical properties of the individual components. Mucosal irritation testing using the Draize method indicates that extremes of acidity and alkalinity predict irritation. However, as demonstrated by the studies of Molhave et al. (*11*) and Koren et al. (*12*), exposure to volatile organic mixtures may also cause irritation, even though each individual component does not. Species differences in the response to irritants also limit interpretation of animal data. For example, a major difference between rodents and higher species is the occurrence of edema in the former in response to irritants (*13*).

Irritation is perceived through stimulation of afferent neurons that are part of the trigeminal nerve. Cain has emphasized interactions between perceived odor and trigeminal stimulation (*14*). The means by which afferent stimulation occurs is less clear. It may be a direct result of nerve fibers interacting with the chemical or an indirect result of locally produced mediators. Data presented below indicate that the epithelium and neurons are key target cells that amplify the response to irritants through the induction of inflammation.

Tobacco Smoke

A challenging scientific problem of great practical importance in the work environment is the observed difference in responsiveness to irritant mixtures in humans. The biologic variability in response may be due to genetic differences, environmental factors, or both. A current focus of interest at the University of Maryland Environmental Research Facility is differential

responsiveness to environmental tobacco smoke among healthy young adults. This topic was chosen for several reasons. Tobacco smoke is an example of a common indoor air pollutant and is a complex mixture. Tobacco smoke is an exposure that most individuals have encountered and recognize. People are usually aware of the nature of their response to exposure. Healthy individuals with no illness or illness behavior report a range of responses to tobacco smoke. Furthermore, as discussed below, animal studies suggest that the response to tobacco smoke is modulated through activation of chemosensitive neurons. An improved understanding of the basis for differential responsiveness to tobacco smoke may enhance our understanding of the basis for differential responsiveness to other irritants.

In our initial studies, a questionnaire was administered to 77 healthy nonsmoking young adults who were being screened for participation in an unrelated study (*16*). Subjects were asked whether they had a history of a group of symptoms associated with environmental tobacco smoke exposure. Nearly 80% reported a history of eye irritation, and more than 30% reported one or more symptom of rhinitis (i.e., rhinorrhea, nasal congestion, or sneezing). Nasal irritation was reported by 18%. This survey was not a population-based study, so no prevalence data should be inferred. However, the study indicated that it was possible to recruit subjects from the community with differential historical responsiveness to environmental tobacco smoke.

We next performed controlled challenge studies comparing 11 environmental tobacco smoke-nonsensitive subjects and 10 environmental tobacco smoke-sensitive subjects (*15*). Subjects were exposed in a climate-controlled facility to 15 min of clean air followed by 15 min of a relatively high concentration of sidestream tobacco smoke (45 ppm CO). Measures of response were symptoms, nasal resistance, and spirometry. On a second study day the protocol was repeated, and measures of response were symptoms and nasal lavage mediators including histamine, albumin, *m*-α-tosyl-L-arginine methyl ester (TAME)-esterase activity, and kinnis.

Significant differences occurred between the historically sensitive and nonsensitive subjects in the symptomatic and nasal resistance response to tobacco smoke challenge. Eye irritation, nasal congestion, rhinorrhea, nose-throat irritation, chest tightness, and cough were all greater in the historically sensitive individuals. Odor perception was comparably elevated in both groups. Symptoms from the 2 study days were significantly correlated. The increase in nasal resistance after tobacco smoke challenge was significantly greater in the environmental tobacco smoke-sensitive subjects compared with the environmental tobacco smoke-nonsensitive subjects (Fig. 1) (*15*). Analysis of proteins and mediators in nasal lavage fluid showed no significant elevations of any of the three mediators or albumin. The absence of elevation in histamine suggested that the response was not an allergic, IgE-mediated response. The absence of elevations of albumin, kinins, and TAME-esterase activity indicated that increased vascular permeability or glandular stimulation did not account for the changes in nasal patency. The results indirectly suggested that changes in vascular tone account for the increased nasal resistance response to tobacco smoke in the sensitive subjects.

Earlier studies of tobacco-smoke-related mucous membrane presence of symptoms of eye, nose, and throat irritation occuring at concentrations of environmental tobacco smoke as low as

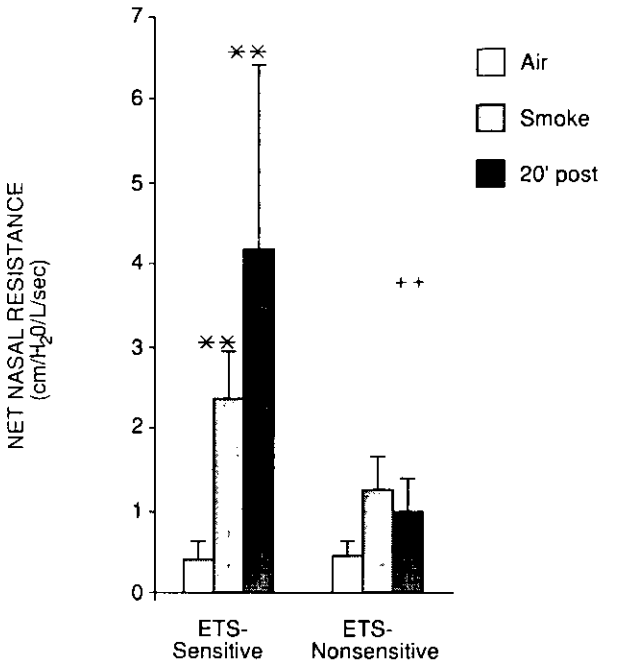

FIGURE 1. Nasal response of environmental tobacco smoke (ETS)-sensitive and environmental smoke-nonsensitive subjects after tobacco smoke challenge (45 ppm CO for 15 min). (**) $p < 0.01$ smoke versus air; (++) $p < 0.01$ ETS-sensitive versus ETS-nonsensitive subjects. Reproduced with permission (*15*).

presence of symptoms of eye, nose, and throat irritation occurring at concentrations of environmental tobacco smoke as low as 1.3 and 2.5 ppm carbon monoxide (*16*). Time-response studies showed that the recognition of odor reached a plateau during the 1-hr exposure, while irritant symptoms continued to rise. Assessment of airway inflammation was not part of their study.

Swedish investigators in the early 1980s examined the possible contribution of c-fiber neurons to the neuroinflammatory response to tobacco smoke (*17–21*). In their experiments, guinea pigs or rats were exposed to tobacco smoke, and inflammation was demonstrated by a variety of means including counting increased nasal wipings and measuring increased Evans Blue dye extravasation (a measure of increased vascular permeability). Filtration of the tobacco smoke (which removed the particles and virtually all the nicotine) did not reduce the response. Pretreatment of the animals with systemic, neonatal capsaicin blocked the response to tobacco smoke, as did local anesthesia or substance P antagonists. These data indicated that the inflammatory irritant response to tobacco smoke occurred through stimulation of c-fiber neurons by the organic, vapor-phase component of tobacco smoke and that release of the neuropeptide substance P was part of the response.

To address the possibility that altered tobacco smoke responsiveness reflected differential function of c-fiber neurons, our study subjects were challenged with a low concentration of capsaicin. Historically environmental tobacco smoke-sensitive subjects reported significantly more rhinorrhea following capsaicin challenge compared with environmental tobacco smoke-nonsensitive subjects (*22*).

Animal studies by Dusser et al. indicate that the respiratory epithelium is both a target of irritant exposures and a modulator

of irritant response (*23*). These investigators measured the effect of aerosolized substance P on guinea pig airway resistance. Under baseline conditions, substance P had little effect on airway tone. Following exposure to cigarette smoke, however, the increase in airways resistance to substance P challenge was markedly augmented. This effect was subsequently demonstrated to be associated with a decrease in neutral endopeptidase in the airway epithelium and to be reversible by the administration of the antioxidant enzyme superoxide dismutase (*23*). The significance of this finding is that it suggests a possible nonspecific, nonimmunologic amplification mechanism for irritants. Simply put, irritants may stimulate c-fiber neurons, causing the release of biologically active neuropeptides. They may simultaneously decrease the presence of epithelial products whose function is to inactivate the neuropeptides. Subsequent exposures to irritants may result in a net increase in neuropeptide release and net increase in inflammation, perhaps culminating in end-organ damage. Further studies are needed to determine whether other irritants or volatile organic compound mixtures will amplify the response to substance P.

In vitro data indicate that the respiratory epithelium is both a target organ and an active respondent to irritants. Leikauf demonstrated that ozone induced an augmentation of eicosanoid metabolism in bovine tracheal epithelial cells (*24*). Products that were released included prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), 6-keto-$PGF_{1\alpha}$, and leukotriene B_4. The increase in $PGF_{2\alpha}$ began as low as 0.1 ppm ozone, a concentration that occurs each summer in most major American cities. Release of epithelial-derived eicosanoids was also demonstrated by Doupnik et al. following *in vitro* exposure to acrolein (*25*).

Acrolein and Ozone

Animal exposure studies have demonstrated that both aldehydes and oxidants cause bronchial hyperresponsiveness and inflammation. Although these are lower respiratory effects, they are important demonstrations of potential effects of irritants on mucosal surfaces. With acrolein, exposure of guinea pigs for 2 hr to 0.3 to 1.26 ppm resulted in an immediate increase in pulmonary resistance and 2- to 3-fold increases in thromboxane B_2 and $PGF_{2\alpha}$ immediately after exposure. Two to 6 hr after exposure there was a 3-fold increase in cholinergic hyperresponsiveness, while lavage neutrophils increased 5-fold 24 hr later.

Human exposure studies have shown upper respiratory mucosal inflammation after controlled challenge with ozone. Graham et al. (*26*) showed a neutrophil influx after ozone challenge in healthy, normal subjects, and Bascom et al. showed a mixed inflammatory cell influx and an increase in nasal lavage albumin after ozone challenge in asymptomatic allergic subjects (*27*). The subjects reported mild nasal irritation at the time the inflammation was observed. Gerrity et al. (*28*) showed that a significant proportion of ozone was removed by the upper respiratory tract of humans, and animal studies by Harkema et al. showed that the upper respiratory tract is an ozone target (*29*).

When mucous membrane irritation complaints occur in relation to building environments, there is usually an absence of abnormalities on routine physical examination and laboratory tests (*5*). But as Kreiss has pointed out "this generalization reflects the conclusions of nonspecialist physicians with a typical diagnostic armamentarium" (*5*). Objective evidence of altered mucosal function has been demonstrated for the eyes, where complaints of eye irritation have been associated with an absence of foam in the eye canthus, decreased stability of precorneal tear film, and epithelial damage documented by slit lamp techniques (*30*).

Few human exposure studies have assessed the health effects of inhaled mixtures on nasal physiology, anatomy, and biology. However, research methods for the study of the upper respiratory tract have expanded tremendously in recent years. Techniques of nasal challenge and analysis of cells and mediators in nasal lavage fluid have proved useful in assessing rhinitis caused by antigens, cold air, and viruses (*31–34*). As described above, measurement of nasal resistance has been used to demonstrate a spectrum of sensitivity to environmental tobacco smoke (*16*). Changes in nonspecific nasal reactivity can be demonstrated after antigen challenge (*35*). Other techniques available for indoor air research include assessing trigeminal sensitivity, ciliary transport, and epithelial permeability (*2*). After development in controlled challenges, it is possible that some of these techniques will be useful for field studies, where the health effects of a complex mixture are being assessed in a specific indoor environment.

New research methods are needed, particularly to evaluate complaints of nasal drying and irritation. One promising approach is that described by Baroody et al. in which filter paper discs are applied to nasal septum and the weight of airway surface fluid determined (*36*). Using this approach, investigators demonstrated a reduction in airway surface fluid in nonallergic subjects 24 hr after ozone exposure (0.4 ppm, 2 hr, intermittent exercise) (*36*). Acoustic rhinometry may prove to be a useful, effort-independent test to assess changes in the anatomy of the upper airway (*37*). Currently, nasal rhinomanometry provides only modest correlations with symptoms of nasal congestion (*38*), and rhinomanometry can be difficult for untrained subjects to perform.

There exists a group of individuals who report a variety of symptoms on exposure to low levels of common volatile organic mixtures such as perfume, cigarette smoke, and soap powders (*39*). Some of these individuals report having occupied "sick buildings" during the time their symptoms began. Studies have demonstrated no alteration in their olfactory threshold, and there is little evidence that an IgE mechanism is responsible for the hyperresponsiveness. Other hypothesized mechanisms include a conditioned response to odors (*40*) and an alteration in trigeminal sensitivity. Critics have been quick to point out that these individuals have "soft" symptoms, meaning that they cannot be validated by objective measures. This is largely true, although many have recognizable diseases such as asthma or vasomotor rhinitis. Additional research is needed to understand the basis of these complaints, their etiology, and treatment.

Research Needs

The research needs presented below are organized by the broad hypothesis to be tested. There is a continuing need for testable hypotheses and improved methodology.

1. Differential responsiveness to irritant mixtures is a common feature of normal healthy populations. Approach: Epidemiological studies: profile responsiveness to irritant mixtures in a working population (e.g., office building). Ask whether individuals responding affirmatively are

"especially sensitive" to typical irritant mixtures. Determine the frequency of individuals responding affirmatively to the question, their population distribution, and the health symptoms they report.

2. Responsiveness to irritant mixtures is an inherited characteristic. Approach: Human challenge studies: controlled challenges to establish whether a distribution of responsiveness exists. Animal studies: challenge studies using inbred strains of mice to determine whether specific physiologic or inflammatory reponses have a genetic basis. Human challenge studies: twin studies (monozygotic versus dizygotic) to determine whether responses observed in animals are similarly determined in humans.
3. Responsiveness to common irritant mixtures may be modified by the presence of commonly occurring, preexisting disease. Approach: Human studies: controlled challenges comparing the response of normal individuals to the response of individuals with allergic rhinitis, vasomotor rhinitis, or atrophic rhinitis. Epidemiologic studies: compare rates of responsiveness between normal people and defined patient groups including groups with and without known mucosal disease (e.g., allergic rhinitis patients compared to those with hypertension).
4. Low-level irritant mixtures will induce airway inflammation. Approach: Animal studies: compare the responses to representative mixtures (e.g., petroleum products, new furnishings, household products, etc.). Human studies: select mixtures and end points based on animal data.
5. Increased historical responsiveness is predictive of an altered inflammatory response. Approach: Human studies: controlled challenge studies, assessing inflammation at mucosal surfaces.
6. *In vitro* studies may predict the irritant potential of VOC mixtures. Approach: *In vitro*: screen a variety of volatile organic compound mixtures using epithelial cells or fibroblasts as target cells and a range of end points (e.g., mediator release, detachment, colony-forming efficiency). Correlate the *in vitro* data with human challenges or animal challenges.
7. Irritant mixtures augment the response to substance P through the depletion of epithelial neutral endopeptidase. Approach: *In vitro*: screen a variety of irritants and volatile organic compound mixtures for their effects on epithelial neutral endopeptidase. Take representative examples and correlate with animal studies [see Dusser et al. (*23*)].
8. Multiple chemical sensitivity is a syndrome that is associated with distinct clinical features. Approach: Epidemiology: establish a case registry using standard survey instruments. Compare features of index cases with a control group from the same clinic. Case evaluation: perform careful clinical evaluations of individuals comparing their health status when in contact and remove from symptom-causing exposures.
9. Populations with symptoms of sick building syndrome will demonstrate increased mucosal inflammation compared with less symptomatic populations. Approach: Bio-epidemiology: Perform nasal lavages or obtain nasal scrapings from populations with differential rates of airway symptoms. Compare the degree of vascular leak (nasal lavage albumin), cellular inflammation (percent neutrophils), and squamous metaplasia (cytologic examination). Analyze epithelial cells via *in situ* hybridization for altered expression of precursors for inflammatory mediators such a cytokines.

In addition to studies such as those described above, basic research on the biology of the airway epithelium is critically important. Research in these areas will elucidate the mediators and other products of these cells. Research will demonstrate how altered morphology (as is seen with chronic irritant exposure) alters the response to irritants. Research in these areas will doubtless provide rich ground for increasingly focused hypotheses on the effects of irritant mixtures on human health.

Considerable effort has been expended on human studies assessing the health effects of exposure to ozone. These studies should be extended to further define the tissue targets of ozone and the alterations in cell biology that occur with ozone exposure. Furthermore, the basis for differential responsiveness to ozone should be explored. The results of these investigations will provide valuable insights as additional studies on the effects of irritant mixtures are designed.

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